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(FILE 'HOME' ENTERED AT 11:21:23 ON 21 FEB 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 11:21:32 ON 21 FEB 2003

L1 7564 S PTHRP OR (PARATHYROID HORMONE RELATED PEPTIDE)
L2 33753 S HYPERCALCEMIA
L3 2248 S L1 AND L2
L4 999 DUP REM L3 (1249 DUPLICATES REMOVED)
L5 522 S L4 AND PY<1996
L6 8898885 S STIMULAT? OR ENHANCE? OR INHIBIT? OR REGULAT?
L7 209 S L5 AND L6
L8 2553805 S (STIMULAT? OR ENHANCE? OR INHIBIT? OR REGULAT?)/TI
L9 54 S L8 AND L5
L10 54 DUP REM L9 (0 DUPLICATES REMOVED)

isolated kidney preparation produced increasing vasodilatation up to 10(-8) M (EC50 of 3 x 10(-9) M) and decreasing responses thereafter. The maximal effect represented 26% of the reference relaxation induced by papaverine. Single injections of hPTHrP-(1-34) resulted in a greater (over 60%) vasodilatation. These results were reminiscent of the tachyphylaxis that occurs after repeated exposure to the peptide. The (3-34) PTH antagonist inhibited the hPTHrP-induced vasodilatation. Human ***PTHrP*** -(1-34) was equipotent with hPTH-(1-34) (EC50 values of 3 x 10(-9) M) but 5-fold less potent than rat (r) PTH-(1-34) in stimulating microvessel adenylate cyclase. GTP enhanced the enzyme responses to the peptides but reduced their potency. Both (3-34) and (7-34) PTH antagonists were inhibitors of hPTHrP- or PTH-stimulated microvascular adenylate cyclase. Synthetic hPTHrP-(1-16) had neither vasodilator nor adenylate cyclase-stimulating activity. This hPTHrP fragment exhibited some inhibitory effect on the hPTHrP-(1-34)-induced stimulation of microvessel adenylate cyclase. These results indicate that hPTHrP possesses PTH-like activity to cause vasorelaxation and to stimulate microvascular adenylate cyclase in the kidney.

L10 ANSWER 53 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1988:325213 BIOSIS
DOCUMENT NUMBER: BR35:30547
TITLE: COMPARATIVE EFFECTS OF PARATHYROID HORMONE PTH OR TUMOR-ASSOCIATED PTH-RELATED PEPTIDE ***PTHRP*** ON RENAL ADENYLATE CYCLASE- ***STIMULATING*** AND BONE RESORPTION ACTIVITIES.
AUTHOR(S): KUKREJA S C; WIMBISCUS S; SHEVRIN D H
CORPORATE SOURCE: DEP. MED., VA WEST. SIDE, ILL., USA.
SOURCE: FORTY-FIFTH ANNUAL NATIONAL MEETING OF THE AMERICAN FEDERATION FOR CLINICAL RESEARCH, WASHINGTON, D.C., USA, APRIL 29-MAY 2, 1988. CLIN RES, (1988) 36 (3), 485A.
CODEN: CLREAS. ISSN: 0009-9279.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L10 ANSWER 54 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:149003 BIOSIS
DOCUMENT NUMBER: BR36:71044
TITLE: PTH RELATED PEPTIDE IS A POTENT ANTIPROLIFERATION AND DIFFERENTIATION FACTOR PTH 7-34 ***INHIBITS*** THE ANTIPROLIFERATIVE AND MATURATION ACTIVITY OF BOTH ***PTHRP*** AND 1 25 DIHYDROXYVITAMIN D-3.
AUTHOR(S): HOLICK M F; NUSSBAUM S; BERNARDO J; DONOVAN L
CORPORATE SOURCE: BOSTON UNIV. SCH. MED., BOSTON, MASS.
SOURCE: JOINT MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY AND THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, SAN FRANCISCO, CALIFORNIA, USA, JANUARY 29-FEBRUARY 2, 1989. J CELL BIOL, (1988) 107 (6 PART 3), 40A.
CODEN: JCLBA3. ISSN: 0021-9525.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

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(FILE 'HOME' ENTERED AT 11:21:23 ON 21 FEB 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 11:21:32 ON 21 FEB 2003
L1 7564 S PTHRP OR (PARATHYROID HORMONE RELATED PEPTIDE)
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L7 209 S L5 AND L6
L8 2553805 S (STIMULAT? OR ENHANCE? OR INHIBIT? OR REGULAT?)/TI
L9 54 S L8 AND L5
L10 54 DUP REM L9 (0 DUPLICATES REMOVED)

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(FILE 'HOME' ENTERED AT 11:21:23 ON 21 FEB 2003)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 11:21:32 ON 21 FEB 2003

L1 7564 S PTHRP OR (PARATHYROID HORMONE RELATED PEPTIDE)
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L6 8898885 S STIMULAT? OR ENHANCE? OR INHIBIT? OR REGULAT?
L7 209 S L5 AND L6
L8 2553805 S (STIMULAT? OR ENHANCE? OR INHIBIT? OR REGULAT?)/TI
L9 54 S L8 AND L5
L10 54 DUP REM L9 (0 DUPLICATES REMOVED)

LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199508
ENTRY DATE: Entered STN: 19950911
Last Updated on STN: 19970203
Entered Medline: 19950829

AB ***Parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHrP***) is a mediator of cellular growth and differentiation as well as a cause of malignancy-induced ***hypercalcemia*** . Most of the actions of ***PTHrP*** have been attributed to its interaction with a specific cell surface receptor that binds the N-terminal domain of the protein. Here we present evidence that ***PTHrP*** promotes some of its cellular effects by translocating to the nucleolus. Localization of transiently expressed ***PTHrP*** to the nucleolus was dependent on the presence of a highly basic region at the carboxyl terminus of the molecule that bears homology to nucleolar targeting sequences identified within human retroviral (human immunodeficiency virus type 1 and human T-cell leukemia virus type 1) regulatory proteins. Endogenous ***PTHrP*** also localized to the nucleolus in osseous cells in vitro and in vivo. Moreover, expression of ***PTHrP*** in chondrocytic cells (CFK2) delayed apoptosis induced by serum deprivation, and this effect depended on the presence of an intact nucleolar targeting signal. The present findings demonstrate a unique intracellular mode of ***PTHrP*** action and a novel mechanism by which this peptide growth factor may modulate programmed cell death.

L10 ANSWER 3 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:347388 BIOSIS
DOCUMENT NUMBER: PREV199598361688
TITLE: Interleukin-6 ***enhances*** ***hypercalcemia*** and bone resorption mediated by parathyroid hormone-related protein in vivo.
AUTHOR(S): De La Mata, Jose; Uy, Harry L.; Guise, Theresa A.; Story, Beryl; Boyce, Brendan F.; Mundy, Gregory R.; Roodman, G. David (1)
CORPORATE SOURCE: (1) Research Services, Audie Murphy VA Hospital, 7400 Merton Minter Boulevard, San Antonio, TX 78284 USA
SOURCE: Journal of Clinical Investigation, (1995) Vol. 95, No. 6, pp. 2846-2852.
ISSN: 0021-9738.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Tumors frequently induce the multifunctional cytokine IL-6, which has been linked to several paraneoplastic syndromes, most notably cachexia. IL-6 stimulates osteoclast formation, causes mild ***hypercalcemia*** , and is produced by bone cells in vitro upon exposure to systemic hormones. Since IL-6 is produced together with parathyroid hormone-related protein (PTH-rP) in some patients with cancer, we tested the hypothesis that production of IL-6 potentiates the effects of PTH-rP on Ca-2+ homeostasis and osteoclastic bone resorption and examined potential mechanisms for these interactions in vivo. Chinese hamster ovarian (CHO) cells stably transfected with cDNAs for IL-6 (CHO/IL-6) and ***PTHrP*** sense (CHO/PTH-rP) or antisense (CHO/PTH-rP AS) were inoculated intramuscularly into nude mice. Experimental groups included CHO/IL-6 plus CHO/PTH-rP; CHO/IL-6 plus CHO/PTH-rP AS; CHO/IL-6 alone; and CHO/PTH-rP alone. Blood ionized Ca-2+ was measured on days 0, 7, 10, 12, and 13. Three different developmental stages in the osteoclast lineage were examined at day 13: the early multipotential precursor, granulocyte macrophage colony-forming units (CFU-GM); more mature mononuclear osteoclast precursors, assessed by their capacity to form tartrate-resistant acid phosphatase-positive multinucleated cells in marrow cultures; and mature osteoclasts, assessed by histomorphometry. IL-6 increased CFU-GM but not bone resorption or Ca-2+. In contrast, PTH-rP induced ***hypercalcemia*** and bone resorption and increased multinucleated osteoclasts and more mature precursors cells, but not CFU-GM. However, mice treated with both IL-6 and PTH-rP had very marked ***hypercalcemia*** and osteoclastosis as well as an increase in the number of both CFU-GM and mature osteoclast

precursors. These data demonstrate that IL-6 enhances PTH-rP-mediated ***hypercalcemia*** and bone resorption, most likely by increasing the pool of early osteoclast precursors that in turn can differentiate to mature osteoclasts. We conclude that IL-6 stimulatory effects on osteoclast precursors may enhance the effects of other bone resorption factors that act at later stages in the osteoclast lineage.

L10 ANSWER 4 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:347696 BIOSIS
DOCUMENT NUMBER: PREV199598361996
TITLE: ***Inhibition*** of parathyroid hormone-related protein release by extracellular calcium in dispersed cells from human parathyroid hyperplasia secondary to chronic renal failure and adenoma.
AUTHOR(S): Matsushita, Hiroshi (1); Hara, Mitsuru; Kuroda, Kazuho Honda Masaiko; Usui, Mitsuko; Nakazawa, Hideki; Hara, Shigelo; Shishiba, Yoshimasa
CORPORATE SOURCE: (1) Dep. Pathol. Toranomon Hosp., Toranomon 2-2-2, Minato-Ku, Tokyo 105 Japan
SOURCE: American Journal of Pathology, (1995) Vol. 146, No. 6, pp. 1521-1528.
ISSN: 0002-9440.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The relationship between parathyroid hormone-related protein (***PTHrP***) release from parathyroid cells and extracellular calcium ion concentration was investigated in three cases of parathyroid hyperplasia secondary to chronic renal failure and in four cases of parathyroid adenoma. Amounts of PTNrP released from individual parathyroid cells dispersed from surgical specimens were estimated by cell immunoblot assay. Parathyroid cells from both hyperplasias and adenomas showed significant suppression in the release of ***PTHrP*** with increase in extracellular calcium ions, but the amounts of ***PTHrP*** released from adenoma cells were significantly larger than from hyperplasia cells. The maximal value for ***PTHrP*** released within 120 minutes from adenoma cells was 2.91 +- 2.11 times 10-2 fmol/cell ((Ca-2+), 0.4 mmol/L), and the minimal value was 1.32 +- 0.35 times 10-2 fmol/cell ((Ca-2+), 2.0 mmol/L). On the other hand, the maximal value for ***PTHrP*** released from hyperplasia cells was 1.73 +- 1.56 times 10-2 fmol/cell ((Ca-2+), 0.4 mmol/L), and the minimal value was 0.32 +- 0.13 times 10-2 fmol/cell ((Ca-2+), 2.0 mmol/L). These results demonstrate actual release of ***PTHrP*** from abnormal parathyroid tissues into the extracellular space with the response to extracellular calcium ions depending on the cell status. Given the lack of definite histological criteria to differentiate between hyperplasias and adenomas in the parathyroid gland, the presently demonstrated significant difference in the ability to release ***PTHrP*** is important in pointing to parathyroid hyperplasia secondary to chronic renal failure as a distinct pathological entity separate from parathyroid adenoma.

L10 ANSWER 5 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:167001 BIOSIS
DOCUMENT NUMBER: PREV199598181301
TITLE: Carboxyl-terminal peptides from parathyroid hormone-related protein ***stimulated*** osteoclast-like cell formation.
AUTHOR(S): Kaji, Hiroshi; Sugimoto, Toshitsugu (1); Kanatani, Masanori; Fukase, Masaaki; Chihara, Kazuo
CORPORATE SOURCE: (1) Third Div., Dep. Med., Kobe Univ. Sch. Med., 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650 Japan
SOURCE: Endocrinology, (1995) Vol. 136, No. 3, pp. 842-848.
ISSN: 0013-7227.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The role of the carboxyl (C)-terminal portion of PTH-related protein (***PTHrP***) in bone resorption continues to be controversial. The present study was performed to examine the effect of C-terminal

PTHrP peptides on osteoclast-like cell formation as well as bone resorption in mice. C-Terminal ***PTHrP*** peptides (human (h) ***PTHrP*** -(107-139) and hPTHrP-(107-111); 10-10-10-8 M) stimulated osteoclast-like cell formation in a concentration-dependent manner in osteoblast-containing mouse bone cell cultures. Moreover, osteoclastlike cells newly formed by these peptides possessed the ability to form pits on the dentine slices. The conditioned medium from UMR-106 cells and MC3T3-E1 cells pretreated with the C-terminal peptides did not affect osteoclast-like cell formation from mouse hemopoietic blast cells derived from spleen cells. The C-terminal peptides as well as hPTHrP-(1-34) stimulated osteoclast-like cell formation from mouse hemopoietic blast cells in the absence of osteoblasts, although both amino- and C-terminal peptides were unable to support hemopoietic blast cells. Protein kinase-C inhibitors (H-7 and staurosporine) almost completely inhibited the stimulation of osteoclast-like cell formation by the C-terminal peptides in both the presence and absence of osteoblasts. The C-terminal peptides did not affect bone resorption by mature osteoclasts in osteoblast-containing mouse bone cell cultures. The present study indicates that C-terminal PTHrP peptides ***possess*** the ability to stimulate osteoclast-like cell formation in both the presence and absence of osteoblasts, possibly through the pathway involving protein kinase-C activation.

L10 ANSWER 6 OF 54 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 95341202 EMBASE
DOCUMENT NUMBER: 1995341202
TITLE: Vascular actions of the calcium- ***regulating*** hormones.
AUTHOR: Bukoski R.D.; Ishibashi K.; Bian K.
CORPORATE SOURCE: Hypertension/Vascular Research Sec., 8.104 Medical Research Bldg, University of Texas Medical Branch,Galveston Island, TX 77555-1065, United States
SOURCE: Seminars in Nephrology, (1995) 15/6 (536-549). ISSN: 0270-9295 CODEN: SNEPDJ
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The vascular actions of the hormones that participate in the regulation of whole animal calcium (Ca2+) homeostasis and related factors are discussed. Parathyroid hormone (PTH) has vasodilator activity that is mediated by a specific cell membrane receptor coupled to adenylate cyclase and thus increases intracellular cAMP and lowers intracellular Ca2+. The peptide may also block voltage-sensitive Ca2+ channels. However, the general consensus is that PTH does not achieve sufficient levels in the serum to modulate vascular reactivity. Parathyroid hormone does, however, share a common receptor and N-terminal amino acid sequence homology with ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHrp***), which has many of the properties of a locally acting vascular regulator. Exciting actions of the steroid hormone, 1,25(OH)2 vitamin D3, have recently been described which suggest that the hormone is a vascular smooth muscle-differentiating agent and promises to set the stage for learning about the long-term modulatory actions of other steroid hormones. Calcitonin has minimal vascular actions, and although CGRP is not classifiable as a Ca2+-regulating hormone, it is a potent vasodilator neurotransmitter. Finally, within the past 2 years there has been s ground swell of activity surrounding the existence of the extracellular Ca2+ receptor that senses changes in interstitial Ca2+. The response of the smooth muscle cell to extracellular Ca2+ is discussed in the context of this receptor.

L10 ANSWER 7 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:551014 BIOSIS
DOCUMENT NUMBER: PREV199698565314
TITLE: ***Inhibition*** of processing of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** by

anti-sense furin: Effect in vitro and in vivo on rat Leydig (H-500) tumor cells.

AUTHOR(S): Liu, Bin; Amizuka, Norio; Goltzman, David; Rabbani, Shafaat A. (1)

CORPORATE SOURCE: (1) Calcium Res. Lab., Rm. H4-72, Royal Victoria Hosp., 687 Pine Ave. West, Montreal, PQ H3A 1A1 Canada

SOURCE: International Journal of Cancer, (1995) Vol. 63, No. 2, pp. 276-281.
ISSN: 0020-7136.

DOCUMENT TYPE: Article

LANGUAGE: English

AB To attain full biological activity, the precursor pro- ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (ProPTHRP) must be converted to the mature peptide ***PTHRP*** . We have examined the effect of inhibiting expression of the pro-hormone convertase furin in H-500 rat Leydig tumor cells on ***PTHRP*** production and action in vitro and in vivo. H-500 Leydig tumor cells were stably transfected with a mammalian expression plasmid containing furin cDNA in an anti-sense orientation. This resulted in inhibition of endogenous furin mRNA expression and of protein production as assessed by immunocytochemistry. These experimental cells secreted extended NH-2-terminal ***PTHRP*** forms with reduced adenylate cyclase-stimulating activity. This was associated with a marked decrease in the proliferation of these tumor cells in vitro. Transfected and control cells were then implanted into male Fischer rats. Animals implanted with control cells became hypercalcemic. In contrast, animals implanted with experimental cells maintained near normal levels of plasma calcium. Experimental cells inoculated in vivo developed into tumors of significantly decreased volume compared to control cells and animal survival time was prolonged. Our results indicate that alteration of the processing of ***PTHRP*** can diminish the hypercalcemic endocrine actions of ***PTHRP*** and can reduce autocrine/paracrine effects of ***PTHRP*** on tumor cell growth both in vitro and in vivo. Furin may also exert a broader role in processing other factors required for tumor proliferation. Consequently, anti-sense modulation of furin activity may be a potential modality for understanding the mechanism of neoplastic growth and progression.

L10 ANSWER 8 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1995:151211 BIOSIS

DOCUMENT NUMBER: PREV199598165511

TITLE: ***Inhibition*** of tumor growth and development of ***hypercalcemia*** by antisense furin in H-500 Leydig tumor cells in vivo.

AUTHOR(S): Liu, B. (1); Goltzman, D.; Rabbani, S. A.

CORPORATE SOURCE: (1) Dep. Med. Physiol., McGill Univ., Montreal, PQ Canada

SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1995) Vol. 36, No. 0, pp. 86.
Meeting Info.: Eighty-sixth Annual Meeting of the American Association for Cancer Research Toronto, Ontario, Canada March 18-22, 1995
ISSN: 0197-016X.

DOCUMENT TYPE: Conference

LANGUAGE: English

L10 ANSWER 9 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1995:142068 BIOSIS

DOCUMENT NUMBER: PREV199598156368

TITLE: Parathyroid hormone-related protein (***PTHrP***) expression by squamous carcinomas and normal keratinocytes: Differential ***regulation*** in vitro.

AUTHOR(S): Rosol, T. J.; Werkmeister, J. R.; Grone, A.; Weckmann, M. T.; Capen, C. C.

CORPORATE SOURCE: Ohio State Univ., Columbus, OH 43210 USA

SOURCE: Modern Pathology, (1995) Vol. 8, No. 1, pp. 56A.
Meeting Info.: Annual Meeting of the United States and Canadian Academy of Pathology Toronto, Ontario, Canada March 11-17, 1995

ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950510
Last Updated on STN: 19990129
Entered Medline: 19950501

AB ***Hypercalcemia*** and leukocytosis are often associated with primary lung cancer as a paraneoplastic syndrome. Recently, parathyroid hormone-related protein (***PTHrP***) and granulocyte colony stimulating factor (G-CSF) have been identified as major causative peptides for ***hypercalcemia*** and leukocytosis, respectively. We studied four men with advanced primary lung cancer (stages from IIIA to IV) who presented with ***hypercalcemia*** (corrected serum calcium levels: 10.5 mg/dl) and leukocytosis (WBC > 10,000 per mm3). The age of the patients ranged from 59 to 79 years old. The pathological subtypes were squamous cell carcinoma in three and adenocarcinoma in one. The mean serum calcium levels and leukocyte counts were 15.8 +/- 1.4 mg/dl (mean +/- SE) and 24,800 +/- 3,253 cells/mm3 (mean +/- SE), respectively. Abnormally high serum levels of ***PTHrP*** and G-CSF were found in three patients (mean +/- SE: 137 +/- 68 pg/ml; normal range in human serum, < 16 pg/ml), and in all four (mean +/- SE: 72 +/- 7.7 pg/ml; normal range in human serum, < 20 pg/ml), respectively. Immuno-histochemical examination of cancerous tissue obtained from these patients showed positive staining for both ***PTHrP*** and G-CSF within the cytoplasm of all the cancerous tissue. These results suggest that the association of ***hypercalcemia*** and leukocytosis in patients with advanced primary lung cancer is caused by production of both ***PTHrP*** and G-CSF by cancerous tissue.

L10 ANSWER 12 OF 54 MEDLINE
ACCESSION NUMBER: 95117555 MEDLINE
DOCUMENT NUMBER: 95117555 PubMed ID: 7817798
TITLE: Interleukin-4 ***inhibits*** spontaneous and parathyroid hormone-related protein- ***stimulated*** osteoclast formation in mice.
AUTHOR: Nakano Y; Watanabe K; Morimoto I; Okada Y; Ura K; Sato K; Kasono K; Nakamura T; Eto S
CORPORATE SOURCE: First Department of Internal Medicine, University of Occupational and Environmental Health, Fukuoka, Japan.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1994 Oct)*** 9 (10) 1533-9.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950217
Last Updated on STN: 19970203
Entered Medline: 19950206

AB We examined the in vivo effects of recombinant murine IL-4 (rmIL-4) on spontaneous and stimulated mouse osteoclast formation. EC-GI cells, which produce ***PThrP*** and IL-1 alpha, were explanted in nude mice. These EC-GI cell-bearing nude mice developed ***hypercalcemia*** (4.90 +/- 0.68 mM), and the calcium levels were decreased to near normal (3.48 +/- 0.73 mM, $p < 0.05$) at day 3 by continuous infusion of rmIL-4 at a dose of 7 micrograms/day. When infused with 0.6 nmol/day of ***PTHrP*** (1-34) in ICR mice, rmIL-4 at a dose of 1 or 5 micrograms/day for 3 days caused a marked inhibitory effect on ***hypercalcemia*** induced by ***PTHrP*** (1-34) (3.73 +/- 0.56-2.54 +/- 0.14 mM, $p < 0.01$). However, rmIL-4 alone did not change the serum calcium in mice. Histomorphometric analysis revealed that rmIL-4 inhibits both spontaneous and ***PTHrP*** (1-34)-stimulated osteoclast formation in mice, with a decrease in osteoclastic surface and in the number of osteoclasts per mm bone surface, respectively. We conclude that IL-4 inhibits spontaneous and stimulated bone resorption resulting from inhibition of osteoclast formation and modulates the development of humoral ***hypercalcemia*** of malignancy.

Last Updated on STN: 19970203
Entered Medline: 19941129

AB Parathyroid hormone (PTH) plays a central role in regulation of calcium metabolism. For example, excessive or inappropriate production of PTH or the related hormone, parathyroid hormone related protein (***PTHrP***), accounts for the majority of the causes of ***hypercalcemia*** . Both hormones act through the same receptor on the osteoblast to elicit enhanced bone resorption by the osteoclast. Thus, the osteoblast mediates the effect of PTH in the resorption process. In this process, PTH causes a change in the function and phenotype of the osteoblast from a cell involved in bone formation to one directing the process of bone resorption. In response to PTH, the osteoblast decreases collagen, alkaline phosphatase, and osteopontin expression and increases production of osteocalcin, cytokines, and neutral proteases. Many of these changes have been shown to be due to effects on mRNA abundance through either transcriptional or post-transcriptional mechanisms. However, the signal transduction pathway for the hormone to cause these changes is not completely elucidated in any case. Binding of PTH and ***PTHrP*** to their common receptor has been shown to result in activation of protein kinases A and C and increases in intracellular calcium. The latter has not been implicated in any changes in mRNA of osteoblastic genes. On the other hand activation of PKA can mimic all the effects of PTH; protein kinase C may be involved in some responses. We will discuss possible mechanisms linking PKA and PKC activation to changes in gene expression, particularly at the nuclear level.

L10 ANSWER 15 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:293514 BIOSIS
DOCUMENT NUMBER: PREV199497306514
TITLE: Cyclic mechanical stretch ***enhances*** angiotensin II (AII)-induced parathyroid hormone: Related protein (***PTHrP***) mRNA expression in vascular smooth muscle cells (VSMCs.
AUTHOR(S): Noda, Masakuni (1); Katoh, Tetsuo; Kurokawa, Kiyoshi; Kumada, Mamoru; Takuwa, Yoh (1)
CORPORATE SOURCE: (1) Dep. Cardiovascular Biology, Tokyo 113 Japan
SOURCE: Japanese Journal of Pharmacology, (1994) Vol. 64, No. SUPPL. 1, pp. 163P.
Meeting Info.: 67th Annual Meeting of the Japanese Pharmacological Society Kyoto, Japan March 21-24, 1994
ISSN: 0021-5198.
DOCUMENT TYPE: Conference
LANGUAGE: English

L10 ANSWER 16 OF 54 MEDLINE
ACCESSION NUMBER: 95160474 MEDLINE
DOCUMENT NUMBER: 95160474 PubMed ID: 7857076
TITLE: [***Regulation*** of synthesis and secretion of parathyroid hormone (PTH) and of tumor ***hypercalcemia*** hormone (***PTHrP***)]. ***Regulation*** de la synthese et de la secretion de l'hormone parathyroidienne (PTH) et de l'hormone hypercalcemiante des tumeurs (***PTHrP***).
AUTHOR: Peraldi M N
CORPORATE SOURCE: Service de Nephrologie A, Hopital Tenon, Paris.
SOURCE: ANNALES D ENDOCRINOLOGIE, ***(1994)*** 55 (5) 127-31.
Ref: 25
Journal code: 0116744. ISSN: 0003-4266.
PUB. COUNTRY: France
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: French
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199503
ENTRY DATE: Entered STN: 19950322
Last Updated on STN: 19950322

through transcriptional and post-transcriptional mechanisms. In addition, ***PTHrP*** modulates the effect of angiotensin II on SMC proliferation. This suggests that ***PTHrP*** acts locally in SMC, possibly to oppose the vasoactive and/or growth-promoting effects of vasoconstrictor agents such as angiotensin II.

L10 ANSWER 20 OF 54 MEDLINE
ACCESSION NUMBER: 93215536 MEDLINE
DOCUMENT NUMBER: 93215536 PubMed ID: 8462465
TITLE: ***Regulation*** of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** production in vitro by the rat hypercalcemic Leydig cell tumor H-500.
AUTHOR: Liu B; Goltzman D; Rabbani S A
CORPORATE SOURCE: Department of Medicine, McGill University, Montreal, Quebec, Canada.
SOURCE: ENDOCRINOLOGY, ***(1993 Apr)*** 132 (4) 1658-64.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930521
Last Updated on STN: 20000303
Entered Medline: 19930430
AB The transplantable rat Leydig cell tumor H-500 is known to cause ***hypercalcemia*** in vivo by the release of abundant PTH-related peptide (***PTHRP***) and to closely reproduce the human syndrome of malignancy-associated ***hypercalcemia*** . In the rat only a single messenger RNA species of 1.4 kilobases is expressed which encodes a peptide of 141 amino acid as the sole molecular form. We have examined in cultured rat Leydig tumor cells H-500, the capacity of multiple factors to regulate ***PTHRP*** messenger RNA expression and secretion. Both fetal bovine serum and epidermal growth factor stimulated ***PTHRP*** gene expression and secretion into conditioned culture medium. Dexamethasone and 1,25-dihydroxyvitamin D3 produced inhibition of ***PTHRP*** gene expression and secretion. Furthermore, in these testicular cells, after 12 h or more of incubation, testosterone produced a dose-dependent (10(-9)-10(-7) M) inhibition of ***PTHRP*** production. No significant difference in this inhibitory response was seen between testosterone and its 5 alpha-reduced metabolite dihydrotestosterone whereas 17 beta-estradiol, progesterone, LH, FSH, and PRL were ineffective. An androgen receptor antagonist Win 49596 blocked the androgen-mediated inhibition of ***PTHRP*** gene expression and secretion, but not that due to dexamethasone. Epidermal growth factor caused an increase, whereas androgen caused a decrease in ***PTHRP*** gene transcription. These studies demonstrated that growth factors, dexamethasone, and 1,25-dihydroxyvitamin D3 are broadly active regulatory agents of ***PTHRP*** production which cross species and tissue barriers. Testosterone may be a more selective modulator which can regulate ***PTHRP*** in tissues such as Leydig cell neoplasms which express the androgen receptor.

L10 ANSWER 21 OF 54 MEDLINE
ACCESSION NUMBER: 93187024 MEDLINE
DOCUMENT NUMBER: 93187024 PubMed ID: 8445039
TITLE: Parathyroid hormone-related protein (***PTHrP***) does not ***regulate*** 1,25-dihydroxyvitamin D serum levels in ***hypercalcemia*** of malignancy.
AUTHOR: Schilling T; Pecherstorfer M; Blind E; Leidig G; Ziegler R; Raue F
CORPORATE SOURCE: Department of Internal Medicine I, Endocrinology and Metabolism, University of Heidelberg, Germany.
SOURCE: JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, ***(1993 Mar)*** 76 (3) 801-3.
Journal code: 0375362. ISSN: 0021-972X.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199304
ENTRY DATE: Entered STN: 19930416
Last Updated on STN: 19930416
Entered Medline: 19930405

AB We investigated in humoral ***hypercalcemia*** of malignancy whether parathyroid hormone-related protein (***PTHrP***) elevation causes a rise in 1,25-dihydroxyvitamin D (1,25-(OH)2 D) serum levels. We assessed 41 patients with ***hypercalcemia*** of malignancy in a prospective study. There were 19 patients who had serum ***PTHrP*** levels in the normal range; 22 patients had elevated serum ***PTHrP*** levels. All patients were treated with the bisphosphonate pamidronate resulting in a drop of serum calcium ($p < 0.0001$) and serum phosphate ($p < 0.0023$) within 12 days, independent of the group. Parathyroid hormone (PTH) was suppressed at the start of therapy and rose to within the normal range during therapy ($p < 0.0001$), regardless of the ***PTHrP*** levels. ***PTHrP*** levels were not influenced by calcium lowering therapy. The serum levels of 1,25-(OH)2 D were either suppressed or in the low normal range at the beginning of the study, without any significant difference between both groups. All patients showed a rise in 1,25-(OH)2 D during bisphosphonate therapy ($p < 0.0001$), independent of their ***PTHrP*** levels. Thus ***PTHrP*** did not influence the calcium, phosphate-, or PTH-dependent regulation of 1,25-(OH)2 D during calcium lowering therapy. We conclude, that ***PTHrP*** does not stimulate renal 1-hydroxylase activity in humoral ***hypercalcemia*** of malignancy.

L10 ANSWER 22 OF 54 MEDLINE
ACCESSION NUMBER: 93289860 MEDLINE
DOCUMENT NUMBER: 93289860 PubMed ID: 8511985
TITLE: Interleukin-1 receptor antagonist ***inhibits*** the ***hypercalcemia*** mediated by interleukin-1.
AUTHOR: Guise T A; Garrett I R; Bonewald L F; Mundy G R
CORPORATE SOURCE: University of Texas Health Science Center, San Antonio.
CONTRACT NUMBER: AR28149 (NIAMS)
CA-40035 (NCI)
DE08569 (NIDCR)
+
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1993 May)***
8 (5) 583-7.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199307
ENTRY DATE: Entered STN: 19930723
Last Updated on STN: 20000303
Entered Medline: 19930709

AB Recently, the effects of interleukin-1 (IL-1) on bone resorption in organ culture have been shown to be inhibited by an interleukin-1 receptor antagonist (IL-1RA), a novel monocyte cytokine in the IL-1 family. IL-1RA, which binds to IL-1 receptors and inhibits many of the effects of IL-1 alpha and beta, has been purified, cloned, and expressed. We used IL-1RA to investigate its effects on calcium homeostasis in vivo. After confirming that IL-1RA completely inhibited the effects of IL-1 on bone resorption in organ cultures, we tested the effects of IL-1RA on ***hypercalcemia*** mediated by IL-1 in normal mice and found that prolonged ***hypercalcemia*** provoked by IL-1 was completely inhibited by IL-1RA. The initial transient decrease in blood ionized calcium observed following an injection of IL-1 was also abrogated. IL-1RA had no effect alone on blood ionized calcium or on ***hypercalcemia*** mediated by parathyroid hormone (PTH) or PTH-related protein (***PTHrP***). These data suggest that antagonists to the IL-1 receptor may provide a useful therapeutic approach to osteoclastic bone resorption

and ***hypercalcemia*** that is IL-1 dependent.

L10 ANSWER 23 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1993:498517 BIOSIS
DOCUMENT NUMBER: PREV199396122524
TITLE: Role of dual signal transduction systems in the ***stimulation*** of bone resorption by ***parathyroid*** ***hormone*** - ***related*** ***peptide*** : The direct involvement of cAMP-dependent protein kinase.
AUTHOR(S): Kaji, Hiroshi (1); Sugimoto, T.; Fukase, M.; Chihara, K.
CORPORATE SOURCE: (1) Third Div., Dep. Med., Kobe Univ. Sch. Med., 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650 Japan
SOURCE: Hormone and Metabolic Research, (1993) Vol. 25, No. 8, pp. 421-424.
ISSN: 0018-5043.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The present study was performed to compare the effect of ***parathyroid*** ***hormone*** - ***related*** ***peptide*** (***PTHrP***) on bone resorption with that of parathyroid hormone (PTH) and clarify the participation of ***PTHrP*** -responsive dual signal transduction systems involving cAMP-dependent protein kinase (PKA) and calcium/protein kinase C (Ca/PKC) in the stimulation of bone resorption by ***PTHrP*** . Bone resorbing activity was estimated as the number of pits formed on the dentine slice and total area of pits per slice in bone cells derived from 2 week-old mice. Human (h) ***PTHrP*** (1-34) (10-7 M) stimulated bone resorption as potent as hPTH-(1-34) (10-7 M) did. The stimulation of bone resorption by hPTHrP-(1-34) and hPTH-(1-34) was equally blocked by either simultaneous treatment with 10-8M eel calcitonin or pretreatment with 10-7 M (Nle-8,18Tyr-34)hPTH(3-34)amide. Rp-cAMPS, an antagonist in the activation of PKA, equally attenuated bone resorption stimulated by ***PTHrP*** as well as by PTH. A23187 (10-7 M) caused a significant stimulation of bone resorption. These findings indicate the direct involvement of PKA activation and a contributory role of an increase in cytosolic calcium in the stimulation of bone resorption by ***PTHrP*** and suggest that ***PTHrP*** stimulates bone resorption presumably through the same mechanism as PTH does.

L10 ANSWER 24 OF 54 MEDLINE
ACCESSION NUMBER: 93390061 MEDLINE
DOCUMENT NUMBER: 93390061 PubMed ID: 8377475
TITLE: ***Regulation*** of parathyroid hormone-related protein production by a squamous carcinoma cell line in vitro.
AUTHOR: Merryman J I; Capen C C; McCauley L K; Werkmeister J R; Suter M M; Rosol T J
CORPORATE SOURCE: Department of Veterinary Pathobiology, Ohio State University College of Veterinary Medicine, Columbus.
CONTRACT NUMBER: CA-08688 (NCI)
R29-AR40220 (NIAMS)
SOURCE: LABORATORY INVESTIGATION, ***(1993 Sep)*** 69 (3) 347-54.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199310
ENTRY DATE: Entered STN: 19931105
Last Updated on STN: 20000303
Entered Medline: 19931018
AB BACKGROUND: Humoral ***hypercalcemia*** of malignancy is a paraneoplastic syndrome associated with a variety of solid neoplasms including squamous cell carcinomas of various sites. Parathyroid hormone-related protein (***PTHrP***) is a newly recognized hormone that has been implicated as one of the major causative factors in the

pathogenesis of this syndrome. A canine oral squamous carcinoma cell line (SCC 2/88) was used to investigate the regulation of production of ***PTHrP*** in response to agents that alter keratinocyte differentiation/proliferation in vitro. EXPERIMENTAL DESIGN: SCC 2/88 cells grown in serum-free media were exposed to various factors and ***PTHrP*** production was measured by radioimmunoassay. This cell line spontaneously produced substantial amounts of ***PTHrP*** (up to 7,000 pg/ml) without the need for a fibroblast-feeder layer. Production of ***PTHrP*** decreased at cellular confluence, and with increasing passage number. RESULTS: Epidermal growth factor, cholera toxin, calcium, 1,25-dihydroxyvitamin D, ionomycin, trans-retinoic acid, transforming growth factor-beta 1 and hydrocortisone stimulated production of ***PTHrP*** by SCC 2/88 cells to various degrees. Transforming growth factor-beta 1 was the most potent stimulator of ***PTHrP*** production, with a maximal stimulation of 25-fold over control. Monensin decreased ***PTHrP*** secretion as early as 6 hours post-treatment and by 48 hours, there was no detectable ***PTHrP*** in the conditioned cell culture medium. Calcium, cholera toxin, ionomycin, and transforming growth factor-beta 1 decreased keratinocyte proliferation as measured by cell counts at all doses tested. CONCLUSIONS: The results of this study revealed that SCC 2/88 cells spontaneously produced substantial amounts of ***PTHrP*** under baseline conditions and that compounds known to affect keratinocyte differentiation/proliferation up-regulated production of ***PTHrP*** . These cells will be valuable to investigate the molecular regulation of ***PTHrP*** production by squamous cell carcinomas.

L10 ANSWER 25 OF 54 MEDLINE
ACCESSION NUMBER: 94039544 MEDLINE
DOCUMENT NUMBER: 94039544 PubMed ID: 8223983
TITLE: Cyclic AMP formation in rat bone and kidney cells is ***stimulated*** equally by parathyroid hormone-related protein (***PTHrP***) 1-34 and PTH 1-34.
AUTHOR: Blind E; Raue F; Knappe V; Schroth J; Ziegler R
CORPORATE SOURCE: Department of Internal Medicine I, Endocrinology and Metabolism, University of Heidelberg, Germany.
SOURCE: EXPERIMENTAL AND CLINICAL ENDOCRINOLOGY, ***(1993)*** 101 (3) 150-5.
Journal code: 8302802. ISSN: 0232-7384.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199312
ENTRY DATE: Entered STN: 19940117
Last Updated on STN: 19980206
Entered Medline: 19931220

AB Parathyroid hormone-related protein (***PTHrP***) plays a major role in the pathogenesis of humoral ***hypercalcemia*** of malignancy. It interacts with the PTH receptor and has therefore a nearly identical effect on bone cells as PTH. However, ***PTHrP*** is thought to be less potent than PTH in stimulating adenylate cyclase in canine renal membranes, leading to the hypothesis of a differential efficiency in signal transduction by ***PTHrP*** with respect to bone vs kidney. In a homologous model with intact osteoblast-like cells (UMR 106) and primary kidney cells, both from the rat, we have tested N-terminal peptide fragments, based on the rat amino acid sequence 1-34, of PTH and ***PTHrP*** . Compared with ***PTHrP*** (1-34), rat PTH(1-34) had a similar relative potency in bone cells (85%) and in kidney cells (140%) in its ability to stimulate adenylate cyclase. Human PTH(1-34) was 5.6- to 6.5-fold less potent than rat PTH(1-34) in both cell types. In human osteoblast-like cells (SaOS-2), rat and human PTH were essentially equally potent compared to ***PTHrP*** (1-34) (identical sequence in rat and human) in stimulating cAMP accumulation. In conclusion, our study revealed the equipotency of rat PTH(1-34) and ***PTHrP*** (1-34) in stimulating intracellular cAMP formation in a homologous system of rat bone and kidney cells. There seemed to be no unique signal transduction mechanism of ***PTHrP*** to the adenylate cyclase in rat kidney cells compared with

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930129
Last Updated on STN: 19970203
Entered Medline: 19921224

AB The gene encoding PTH-related peptide (***PTHrP***) is expressed in a wide variety of normal and neoplastic tissues. Increased ***PTHrP*** gene expression in and secretion of ***PTHrP*** by specific tumors directly contributes to the development of malignancy-associated ***hypercalcemia*** in vivo. To define the genetic elements important for the control of ***PTHrP*** gene transcription, we used the reverse transcription polymerase chain reaction to delineate the control of promoter utilization and the splicing patterns of the exons encoding 5'-untranslated sequences. The majority of normal and neoplastic human tissues contained ***PTHrP*** mRNA transcripts initiating from both the up-stream (P1) and down-stream (P2) human ***PTHrP*** promoters. Furthermore, the downstream promoter was preferentially used by a factor of more than 30-fold. P1-initiated transcripts contained RNA species both with and without exon 2 (E2) sequences, except in the pancreas, adrenal, and stomach, where E2-containing sequences predominated. The transcriptional activities of P1, P2, and P1 + P2 were assessed by transfection of the corresponding ***PTHrP*** -chloramphenicol acetyltransferase (CAT) fusion genes into heterologous cell lines. Fusion genes containing P2 sequences were more transcriptionally active than fusion genes containing P1 sequences. The transcriptional activities of P1 + P2 in their natural tandem orientation were additive in rat keratinocytes and human JEG choriocarcinoma cells. In contrast, the activity of P1 + P2 was less than that of P2 alone in hamster BHK fibroblasts and InR1-G9 cells, and human HeLa cells. Analysis of the transcriptional properties of 5'-deleted human ***PTHrP*** -CAT constructs revealed the presence of multiple positive and negative DNA sequences (within both P1 and P2) functionally important for human ***PTHrP*** gene transcription. Distinct positive and negative DNA elements were also identified from analysis of 5'-deleted rat ***PTHrP*** -CAT fusion genes. The results of these experiments provide evidence for cell- and tissue-specific utilization of 1) distinct human ***PTHrP*** transcription start sites and specific patterns of 5'-exon splicing and 2) multiple positive and negative DNA control elements, important for the regulation of human and rat ***PTHrP*** gene transcription.

L10 ANSWER 30 OF 54 MEDLINE
ACCESSION NUMBER: 93071251 MEDLINE
DOCUMENT NUMBER: 93071251 PubMed ID: 1332431
TITLE: Parathyroid hormone-related protein ***stimulates*** prostaglandin E2 release from human osteoblast-like cells: modulating effect of peptide length.
AUTHOR: Mitnick M; Isales C; Paliwal I; Insogna K
CORPORATE SOURCE: Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut.
CONTRACT NUMBER: AR39571 (NIAMS)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1992 Aug)*** 7 (8) 887-96.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19980206
Entered Medline: 19921217

AB Parathyroid hormone-related protein (***PTHrP***) is a potent bone-resorbing protein that frequently mediates the humoral ***hypercalcemia*** of malignancy syndrome. Since prostaglandins may

DOCUMENT NUMBER: 1992245313
TITLE: ***Inhibition*** of bone resorption by the bisphosphonate BM 21.0955 is not associated with an alteration of the renal handling of calcium in rats infused with parathyroid hormone-related protein.
AUTHOR: Rizzoli R.; Caverzasio J.; Bauss F.; Bonjour J.-P.
CORPORATE SOURCE: Division of Clinical Pathophysiology, Department of Medicine, University Hospital,CH-1211 Geneva 4, Switzerland
SOURCE: Bone, (1992) 13/4 (321-325).
ISSN: 8756-3282 CODEN: BONEDL
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Hypercalcaemia of malignancy is determined by an increase of bone resorption and/or renal tubular reabsorption of calcium (Ca). However, this latter component has been found to vary in certain patients during therapy with bone resorption inhibitors such as bisphosphonates. We investigated the possible effects of the highly potent bisphosphonate BM 21.0955 on the renal handling of Ca in thyroparathyroidectomized rats made hypercalcaemic by the stimulation of both bone resorption and renal tubular reabsorption of Ca induced by the chronic infusion of parathyroid hormone-related protein (***PTHrP***). Dose-dependent inhibition of bone resorption by BM 21.0955, as indicated by the decrease in fasting urinary Ca excretion from 64.0 .+-. 7.3 to 6.7 .+-. 3.1 nmol/ml GFR, was associated with a change in plasma Ca from 2.97 .+-. 0.10 to 2.63 .+-. 0.16 mmol/l. However, the relationship between urinary Ca excretion and plasma Ca was not altered, either at endogenous plasma Ca concentration or during the acute infusion of Ca. Similarly, an index of renal tubular reabsorption of Ca calculated from the slope of the linear portion of the relationship between urinary Ca and plasma Ca, which was increased by ***PTHrP*** administration, was not influenced by BM 21.0955 therapy (2.59 .+-. 0.15 vs. 2.55 .+-. 0.11 mmol/l GFR). These results indicate that BM 21.0955, which is one of the most potent bisphosphonates inhibiting bone resorption, did not affect the renal tubular reabsorption of Ca enhanced by ***PTHrP*** .

L10 ANSWER 33 OF 54 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:166725 CAPLUS
DOCUMENT NUMBER: 116:166725
TITLE: Parathyroid-like ***regulation*** of parathyroid-hormone-related protein release and cytoplasmic calcium in cytotrophoblast cells of human placenta
AUTHOR(S): Hellman, Per; Ridefelt, Peter; Juhlin, Claes; Aakerstroem, Goeran; Rastad, Jonas; Gylfe, Erik
CORPORATE SOURCE: Dep. Surg., Univ. Uppsala, Uppsala, S-751 23, Swed.
SOURCE: Archives of Biochemistry and Biophysics (***1992***), 293(1), 174-80
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunohistochem. staining of human placenta revealed intense reactivity for amino terminal and midregional parathyroid-hormone-related protein (***PTHrp***) in the cytotrophoblast cells and weaker staining in the syncytiotrophoblasts. The cytotrophoblasts also displayed conspicuous surface staining with the monoclonal antibodies E11 and G11, which recognize a Ca2+ receptor mechanism regulating hormone release of parathyroid cells. Cytotrophoblasts enriched on Percoll gradients or by linking surface-bound E11 to magnetic beads revealed biphasic elevation of cytoplasmic Ca2+ ([Ca2+]i) on a stepwise rise of external Ca2+ from 0.5 to 3.0 mM, with a half-maximal effect a 1.75 mM. Individual cytotrophoblasts identified by their E11 reactivity disclosed a temporary increase of [Ca2+]i on elevation of external Mg2+, whereas Mn2+ triggered both a [Ca2+]i transient and an influx of itself. These effects were efficiently

induced ***hypercalcemia*** , relative hypophosphatemia, phosphaturia, and reduced bone mass. Osteoblast number was increased, but osteoclast number was not. Indices of bone formation were unchanged or reduced. The dose of IL-1 alpha chosen had no statistically significant effect, except for reduced longitudinal bone growth, but when combined with ***PTHrP*** , IL-1 alpha reduced ***hypercalcemia*** , hypophosphatemia, and phosphaturia. In contrast to the blood and urine effects, IL-1 alpha did not interact significantly with ***PTHrP*** 's effect on bone measurements. Northern analysis of periosteal cell mRNA showed that ***PTHrP*** reduced expression of osteocalcin, but not glyceraldehyde-3-phosphate dehydrogenase; IL-1 alpha had no additional effect. These data suggest that 1) continuously administered ***PTHrP*** alone may induce uncoupled bone turnover with decreased cortical bone formation; 2) IL-1 alpha appears to inhibit strongly the renal effects of ***PTHrP*** and weakly (if at all) its actions on bone and, thus, to decrease its hypercalcemic, phosphaturic, and hypophosphatemic actions; and 3) cosecretion of IL-1 alpha, and possibly other peptide cytokines, with ***PTHrP*** may modify the clinical expression of HHM.

L10 ANSWER 38 OF 54 MEDLINE
ACCESSION NUMBER: 91094407 MEDLINE
DOCUMENT NUMBER: 91094407 PubMed ID: 1670794
TITLE: ***PTHrP*** : endocrine and autocrine ***regulator*** of calcium.
AUTHOR: Anonymous
SOURCE: LANCET, ***(1991 Jan 19)*** 337 (8734) 146-8.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199102
ENTRY DATE: Entered STN: 19910322
Last Updated on STN: 19950206
Entered Medline: 19910213

L10 ANSWER 39 OF 54 MEDLINE
ACCESSION NUMBER: 92214249 MEDLINE
DOCUMENT NUMBER: 92214249 PubMed ID: 1666809
TITLE: ***Stimulation*** by parathyroid hormone-related protein and transforming growth factor-alpha of phosphate transport in osteoblast-like cells.
AUTHOR: Pizurki L; Rizzoli R; Caverzasio J; Bonjour J P
CORPORATE SOURCE: Department of Medicine, University Hospital of Geneva, Switzerland.
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1991 Nov)*** 6 (11) 1235-41.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199205
ENTRY DATE: Entered STN: 19920515
Last Updated on STN: 19970203
Entered Medline: 19920504
AB Parathyroid hormone (1-34) [PTH-(1-34)] has been shown to stimulate sodium-dependent phosphate transport (NaPiT) in UMR-106 osteoblast-like cells through a cAMP-dependent mechanism. Whether a synthetic amino-terminal fragment of parathyroid hormone-related protein (***PTHrP***) or the full-length molecule, which are recognized to interact with the same receptor as PTH, affect NaPiT in the same way is not known. We investigated and compared the effects of bPTH-(1-34), ***PTHrP*** -(1-34), and ***PTHrP*** -(1-141) on NaPiT and cAMP production in the osteoblastic cell line UMR-106. Each of the three peptides increased cAMP production and exerted a concentration-dependent stimulation of NaPiT after incubation for 4-6 h. We also studied the

hPTH-(1-34) or hPTHrP-(1-34) was inhibited by both [Nle8,18Tyr34]-hPTH-(3-34-)NH2 and [Tyr34]-hPTH-(7-34)-NH2. However, [Nle8,18Tyr34]hPTH-(3-34)-NH2 and [Tyr34]-hPTH-(7-34)-NH2 inhibited hPTH-induced cAMP production more strongly. The inhibitory action of phosphate uptake by hPTH-(1-34) and hPTHrP-(1-34) was prevented in the presence of a 100-fold greater concentration of [Nle8,18Tyr34]hPTH-(3-34)-NH2. The antagonistic action of [Nle8,18Tyr34]hPTH-(3-34)-NH2 on the inhibition of phosphate uptake induced by hPTH-(1-34) and hPTHrP-(1-34) became weaker with time (0-120 minutes), and [Nle8,18Tyr34]hPTH-(3-34)-NH2 did not antagonize the inhibition of phosphate uptake induced by hPTHrP-(1-34) at 120 minutes of incubation. Our results indicated that ***PTHrP*** inhibits renal phosphate transport, at least in part through an adenylate cyclase-cAMP-coupled PTH receptor, but the response to the competitive inhibition of this peptide-induced cAMP production and inhibition of phosphate uptake with PTH receptor antagonists was different. PTH receptor heterogeneity in OK cells may exist and contribute to this phenomenon.

L10 ANSWER 46 OF 54 MEDLINE
ACCESSION NUMBER: 90342607 MEDLINE
DOCUMENT NUMBER: 90342607 PubMed ID: 2166420
TITLE: The synthetic human parathyroid hormone-related protein is ***inhibited*** by a parathyroid hormone antagonist in rats in vivo.
AUTHOR: Horiuchi N; Hongo T; Clemens T L
CORPORATE SOURCE: Division of Endocrinology, Cedars-Sinai Medical Center/UCLA 90048.
CONTRACT NUMBER: AR 36446 (NIAMS)
AR 39191 (NIAMS)
CA 49053 (NCI)
SOURCE: JOURNAL OF BONE AND MINERAL RESEARCH, ***(1990 Jun)*** 5 (6) 541-5.
Journal code: 8610640. ISSN: 0884-0431.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199009
ENTRY DATE: Entered STN: 19901012
Last Updated on STN: 19901012
Entered Medline: 19900913
AB The structure of a novel protein, parathyroid hormone-related protein (***PTHrP***), secreted by human tumors associated with ***hypercalcemia*** has recently been determined. Administration of a synthetic fragment of this protein in vivo reproduces features of the clinical paraneoplastic syndrome of humoral ***hypercalcemia*** of malignancy and produces biologic responses closely similar to those obtained with parathyroid hormone (PTH). A PTH antagonist designed to reversibly occupy PTH receptors inhibited major actions of the tumor peptide in vivo, including phosphaturia, urinary cAMP excretion, and increased serum ionized calcium. These studies indicate that ***PTHrP*** and PTH mediate their bioactivities through shared receptors in vivo and establish a potential specific mechanism-based approach utilizing PTH antagonists for the therapy of tumor-associated ***hypercalcemia*** .

L10 ANSWER 47 OF 54 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1990:462038 BIOSIS
DOCUMENT NUMBER: BR39:97399
TITLE: ***PTHRP*** ***STIMULATES*** THE PROLIFERATION OF HUMAN BONE CELLS AND MOUSE 3T3 FIBROBLASTS.
AUTHOR(S): GALLAGHER J A; HYMAN J; PENNINGTON S R
CORPORATE SOURCE: DEP. HUMAN ANATOMY AND CELL BIOL., UNIV. LIVERPOOL.
SOURCE: SYMPOSIUM ON BONE CELL BIOLOGY, PHYSIOLOGY, AND PATHOLOGY, ELMSFORD, NEW YORK, USA, DECEMBER 1, 1989. BONE (ELMSFORD), (1990) 11 (3), 225.
CODEN: BONEDL. ISSN: 8756-3282.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD

Last Updated on STN: 19970203
Entered Medline: 19900425

AB A PTH-related peptide (***PTHRP***) has been identified and its cDNA cloned from tumors associated with the syndrome of humoral ***hypercalcemia*** of malignancy. The ***PTHRP*** and PTH genes appear to represent members of a gene family. Whereas the PTH gene is expressed exclusively in the parathyroids, the ***PTHRP*** gene appears to be widely expressed, but little is known concerning the regulation of its expression in any site. We studied the regulation of ***PTHRP*** gene expression in a human carcinoid cell line (NCI-H727) which has neuroendocrine features and also produces calcitonin, calcitonin gene-related peptide, and chromogranin-A. We found that the synthetic glucocorticoid triamcinolone produced time- and dose-dependent decreases in steady state ***PTHRP*** and calcitonin mRNA levels in NCI-H727 cells. This effect was blocked by the competitive glucocorticoid inhibitor RU-486. Messenger RNA stability and transcription run-off experiments revealed that triamcinolone decreased ***PTHRP*** and calcitonin expression by repressing the transcription rates of both genes.

L10 ANSWER 50 OF 54 MEDLINE
ACCESSION NUMBER: 89325177 MEDLINE
DOCUMENT NUMBER: 89325177 PubMed ID: 2752979
TITLE: Hypotension and cardiac ***stimulation*** due to the parathyroid hormone-related protein, humoral ***hypercalcemia*** of malignancy factor.
AUTHOR: Nickols G A; Nana A D; Nickols M A; DiPette D J; Asimakis G K
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston 77550.
CONTRACT NUMBER: HL-34146 (NHLBI)
HL-37943 (NHLBI)
SOURCE: ENDOCRINOLOGY, ***(1989 Aug)*** 125 (2) 834-41.
Journal code: 0375040. ISSN: 0013-7227.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 198908
ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19970203
Entered Medline: 19890829

AB Patients with humoral ***hypercalcemia*** of malignancy display markedly increased serum calcium levels, reduced blood pressure, and tachycardia. The causative agent, humoral ***hypercalcemia*** of malignancy factor [also called PTH-related protein (***PTHrp***)] has been shown to interact with PTH receptors in bone and kidney. We compared human ***PTHrp*** -(1-34) with rat PTH-(1-34) for the effects of each peptide on cardiovascular function in unrestrained conscious rats. Both ***PTHrp*** and PTH decreased blood pressure in a dose-dependent manner over the concentration range of 0.3-30 micrograms/kg. ***PTHrp*** was approximately 3-fold more potent than PTH, producing up to a 50 mm Hg decrease in pressure within 2 min at 10 micrograms/kg. Both peptides increased heart rate more than 70 beats/min at this dose. However, PTH appeared to exert greater efficacy and potency than ***PTHrp*** in increasing heart rate in vivo. In the isolated and perfused rat heart, ***PTHrp*** and PTH produced positive chronotropic and positive inotropic effects as well as increased coronary flow. ***PTHrp*** was more potent and more effective than PTH. The time courses of these effects in the perfused heart preparations indicated that both peptides produced maximal effects within 1 min, with all responses returning to baseline within 10 min. In isolated helical strips of rat aorta, ***PTHrp*** and PTH relaxed norepinephrine-contracted tissues in a concentration-dependent fashion. A functional endothelium was not required for the relaxing effects of either peptide. These studies indicate that ***PTHrp*** and PTH decrease blood pressure by relaxing vascular tissue in an endothelium-independent manner. Also, these peptides directly increased heart rate, contractility, and coronary flow. Since